PHYSIOLOGICAL SIGNALS AND THEIR FRACTAL RESPONSE TO STRESS CONDITIONS, ENVIRONMENTAL CHANGES AND NEURODEGENERATIVE DISEASES

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ABSTRACT

During the last decades nonlinear system theory has been widely applied to the analysis of biomedical time series and given rise to what is known as nonlinear and fractal physiology. Some of these studies have been intended to develop more reliable methodologies for understanding how biological systems respond to peculiar altered conditions induced by internal stress, environment stress and/or disease. Herein, we show some of our results regarding the fractal dependency on different conditions of physiological signals such as inter-breath intervals, heart inter-beat intervals and human stride intervals.

1. INTRODUCTION

Physiological phenomena have been studied by means of averages, histograms and simple power spectra of a physiological variable. More recently the focus of analysis has shifted to the study of the patterns in the fluctuations of the variable. These fluctuations are not as simple as random stochastic phenomena but present fractal properties [West and Goldberger, 1987; West, 1990; Goldberger et al., 1990; Bassingthwaighte et al., 1994]. Indeed, physiological time series are found to exhibit complex autocorrelation patterns suggesting that the dynamics and the structure of the underlying biology are nonlinear, chaotic and/or fractal, either in space, time or both.

Peng et al. [1999] were the first to show that the scaling of the central moments of beat-to-beat intervals or heart rate variability (HRV) time series yield the fractal dimension of the cardiovascular control system. Subsequently HRV time series has been found, rather than being monofractal, to be multifractal [West et al., 1999]. Similarly, walking as described by stride-to-stride interval time series, also called stride rate variability (SRV), has been found to be characterized by fractal [Hausdorff et al., 1995; Hausdorff et al., 1997] and multifractal properties [Scafetta et al., 2003].

2. FRACTAL & MULTIFRACTAL SEQUENCES

Fractal or long-range correlated processes [Mandelbrot, 1983; Feder, 1988] have been classified as 1/f-phenomena, since their time series have power spectra that exhibit an inverse power law with respect to frequency, $P(f)\sim 1/f^{\beta}$. Similarly, the degree of long-range correlation of a time series can be assessed from the Hurst exponent $H=(\beta+1)/2$ and from the fractal dimension $D=2-H$. The algorithms used to estimate the Hurst exponent directly are usually quite simple and stable [Peng et al., 1994; Scafetta and Grigolini, 2002]. A simple algorithm is based on the estimation of the standard deviation of the diffusion process $D(\tau)$ generated by integrating the data of the time series. This function of the diffusion time τ, in the case of long-range correlations, yields a curve of the type $D(\tau)=c\tau^{H}$, where c is an opportune constant and H is the Hurst exponent [Scafetta and Grigolini, 2002].

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The value $H=0.5$ characterizes random sequences which are known as white noise because their power spectrum is flat, $\beta=0$. A value $0<\beta<1$ or $0.5<H<1$ characterizes persistent or long-range correlated sequences, where an event is correlated positively with the previous ones. Thus, persistent sequences are characterized by a stochastically up-up or down-down pattern. A value $\beta=1$ or $H=1$ characterizes pure 1/f-phenomena known in the literature as pink noise. It might be possible to extend the discussion for values $\beta>1$ or $H>1$., which correspond to time series are more properly referred to as *walks*, that is, integrals of noises. The simplest example of a walk is the *random walk,* which is the integral of random noise, that has $\beta=2$ or $H=1.5$. Finally a value $\beta<0$ or $0<H<0.5$ characterizes anti-persistent sequences where each event is correlated negatively with the previous one. Thus, anti-persistent sequences are characterized by a rapid stochastically alternating up-down pattern.

Physiological sequences are usually characterized by a value of the Hurst exponent ranging from $H=0.5$ to $H=1.5$. This finding suggests that biological systems are correlated persistent processes whose dynamics keeps memory of past events. It is largely expected that the Hurst exponent, which measures the strength of this memory, evolves as a response of internal or environment stress, and disease because modified physiological conditions likely affect the dynamics of biological systems.

A higher hierarchy of complexity is shown by multifractal time series. These sequences are characterized by a wide spectrum of fractal dimension [Feder, 1988; Mallat, 1999]. There are also phenomena where local scaling exponents, commonly referred to as local Hölder exponents [Struzik, 2000], change from point to point in the time series. Generally, a full range of the scaling properties of multifractal phenomena is described by a singularity spectrum or a probability distribution of local Hölder exponents. Usually, singularity spectra and local Hölder exponent distributions are determined by data processing techniques based on wavelet transforms [Mallat, 1999; Struzik, 2000; Scafetta et al., 2003]. Another method relies on a multifractal detrended fluctuation analysis [Kantelhardt et al, 2002]. The average Hölder exponent, h_0, is approximately related to the Hurst exponent as $h_0 \approx H-1$ [Scafetta et al., 2003]. The singularity spectrum or the probability distribution of local Hölder exponents are characterized by at least three independent parameters: the position of the maximum, the width and the asymmetry of the singularity spectrum or probability distribution curve. As for the Hurst exponent, these three parameters too are expected to be altered under internal or environment stress and/or disease.

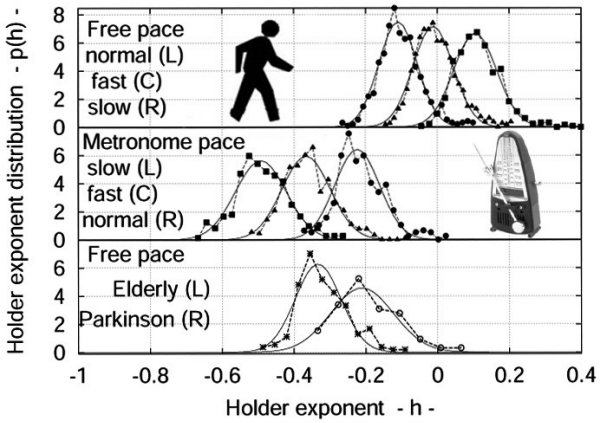

Figure 1: Hölder exponent histograms for the stride interval sequences during free walking and metronome-paced conditions for normal, slow and fast paces and for a normal elderly person and a subject with Parkinson's disease. The histograms are fitted with Gaussian functions. (L=Left, C=Center, R=Right). (Data from http://www.physionet.org).

3. PHYSIOLOGICAL EXAMPLES

In the following we summarize some of our results showing the fractal dependency of physiological time series such as inter-breath intervals, inter-beat (R-R) intervals and human stride intervals on environmental stress and physiological pathologies. Examples regard cases of acute hypobaric hypoxia, progressive central hypovolemia, neurodegenerative diseases, as well as, from different kinds of physical exercises.

Figure 1 shows typical Hölder exponent distributions obtained from human stride interval time series under different conditions. The fractal and multifractal nature of the stride interval fluctuations becomes slightly more pronounced (that is, the Hölder exponent distributions shift toward higher values and become wider) under faster or slower paced frequencies relative to the normal paced frequency of a subject [Scafetta et al., 2003; West and Scafetta, 2003]. In fact, the rationale of this finding is that under this type of stress a subject has to focus on the task and as a consequence the correlation of the physiological system increases. On the contrary, the randomness of the fluctuations increases (the Hölder exponent distributions shift toward the left) if subjects are asked to synchronize their gait with the frequency of a metronome. One interpretation is that the psychological synchronization acts continuously and disrupts the natural physiological temporal correlations of walking.

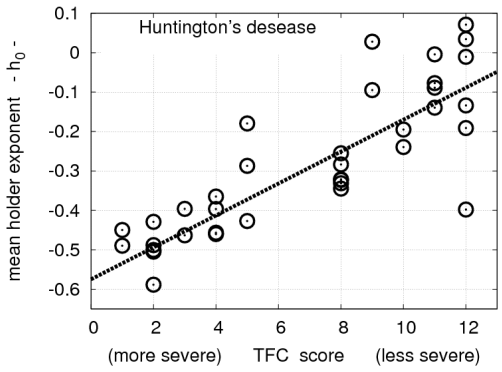

Figure 2: Relationship between mean Hölder exponent and total functional capacity (TFC) score of Unified Huntington's Disease Rating Scale (0 = most impairment; 13 = no impairment). The mean Hölder exponent decreases (that is, the sequences become more random) as the disease severity increases. The two measures are highly correlated (r^2=0.64, P<0.005). (Data from *http://www.physionet.org*).

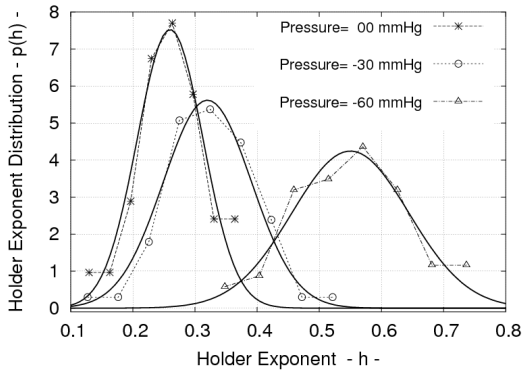

Figure 3: Hölder exponent histograms for R-R interval time series for a patient subjected to progressive central hypovolemia using lower body negative pressure. Data for three different values of the pressure are shown. The histograms are fitted with Gaussian functions.

Figure 1 also suggests that there is an increase of the randomness of the stride interval fluctuations in elderly subjects and those suffering from neurodegenerative disease such as Parkinson's disease. The relation between severity of a neurodegenerative disease and fractal exponents is more evident in Figure 2. Here a group of patients with Huntingdon's disease is studied and the mean Hölder exponent, h_0, for stride interval sequences is found to be strongly correlated with the total functional capacity (TFC) score that measures the severity of impairment. This finding can be explained as a result of neuronal deterioration a network of neurons controlling human locomotion could be expected to become less correlated than a healthy neuronal network, and the leftward shift of the Hölder exponent distribution is expected to increase with the severity of the neurodegenerative disease, as Figure 2 shows.

Figure 3 shows the dependency of the fractal properties of R-R interval time series during progressive central hypovolemia with lower body negative pressure [West et al., 3003]. By increasing the lower body negative pressure these time series became more persistent and the distributions of Hölder exponents became wider. Because physiological responses to lower body negative pressure are similar to those experienced during hemorrhage shock, multifractal analysis may be a powerful tool to predict incipient shock.

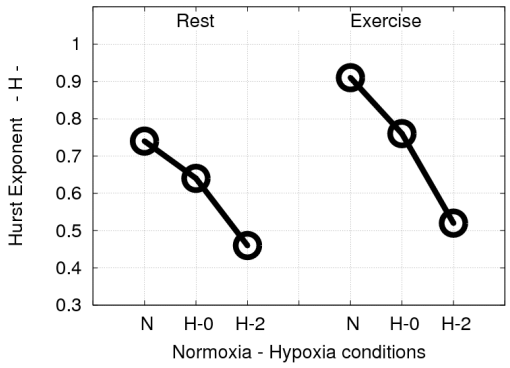

Figure 4: Hurst exponents of inter breath interval sequences for a subject during normoxia (N) and hypoxia in a hypobaric chamber at a simulated altitude of 15,000 feet. H-0 is a measurement at the beginning of the hypoxic exposure; H-2 is after two hours of continuous hypoxia. The analysis is done for a subject at rest and during exercise.

Figure 4 shows results regarding to inter breath interval sequences of a resting normal human volunteer during normoxia and during a 2-hour period of acute hypoxia. These time series exhibit persistence, although after 2 hours of hypoxia inter breath interval time series tended to become more random, or less correlated, as indicated by a decrease in the value of the Hurst exponent. This finding suggests that respiratory rhythm generation is disrupted by sudden acute hypoxia. If the same individual are asked to exercise for approximately ten minutes during each condition, inter breath interval sequences became more random during acute hypoxia but for each

condition the sequences were more persistent (higher values of the Hurst exponent) than at rest. The latter finding is an equivalent physiological response to what we have observed for the stride interval sequences (Figure 1), that become more persistent during exercise. This suggests that, in general, forced exercise induces an increase of the dynamical correlation of a physiological system. Thus, we can hypothesize that fractal analysis might be a useful tool with which to probe mechanisms involved in control of breathing under different environmental conditions.

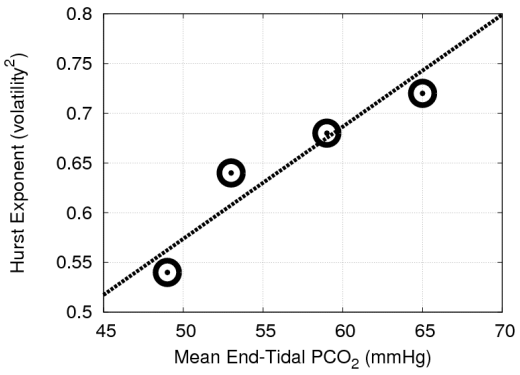

Figure 5: Mean Hurst exponent for the square of the volatility index of the inter breath interval sequence for the first 36 hours after upper abdominal surgery in 4 patients. The Hurst exponent is highly correlated with mean end-tidal PCO2 (r=0.93, P=0.008). Each point represents one patient.

Figure 5 shows the results regarding a preliminary study where we analyzed postoperative inter breath interval sequences of a small group of patients for the purpose of determining whether the Hurst exponent of these sequences could be correlated with respiratory depression, as indicated by a high end-tidal PCO_2. Conventional wisdom indicates that respiratory depression is associated with a low respiratory rate. On the contrary, we have found that respiratory rate can be misleading. However, a significant correlation exists between mean end-tidal PCO_2 pressure and Hurst exponent value of the square of the volatility of the inter breath interval sequences (volatility is herein defined as the difference between two consecutive inter breath intervals). This study suggest the possibility of developing a novel diagnostic strategy based on the simple study of a relatively inexpensive and non-invasive continuous monitoring of inter breath interval. In fact, continuous monitoring of arterial blood PCO_2 is impractical, and measurement of end-tidal PCO_2 inaccurate.

4. CONCLUSIONS

The rationale of these finding is that the central nervous system is capable of firing at time intervals whose sequences present persistent correlation patterns. However, the intensity of the autocorrelation of the actual neural firing time intervals is expected to be influenced by both a change of internal neural correlation among the nervous firing centers and/or a change in peripheral feedback. These physiological responses to stress or environmental changes can be modeled by a simple stochastic central pattern generator that ideally reproduces the control system, which then drives respiratory neurons, causing contraction of respiratory muscles, producing a cyclical output [West and Scafetta, 2003].

In conclusion, we find that fractal and multifractal analysis of physiological signals might facilitate understanding of complex physiological systems and, as a direct consequence, could help develop novel clinical strategies for diagnosing pathology and detecting adverse events.

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REFERENCIES

Bassingthwaighte J.B., L.S. Liebowitch and B.J. West, 1994: *Fractal Physiology*, Oxford University Press, Oxford.

Goldberger A.L., D.R. Rigney, and B.J. West, 1990: Chaos, fractals and physiology, *Scientific American* 262, 42-49.

Feder J., 1988: *Fractals,* Plenum Press, New York.

Hausdorff J.M., Peng C.-K., Ladin Z., Wei J.Y., Goldberger A.L., 1995: Is Walking a Random-walk-Evidence for Long-range Correlations in Stride Interval of Human Gait*, J. Appl. Physiol.* **78 (1),** 349-358.

Hausdorff J.M., Mitchell S.L., Firtion R, Peng C.-K., Cudkowicz M.E., Wei J.Y., Goldberger A.L., 1997: Altered fractal dynamics of gait: reduced stride-interval correlations with aging and Huntington's disease, *J Applied Physiology* **82**, 262-269.

Kantelhardt J. W., S. A. Zschiegner, E. Koscielny-Bunde, S. Havlin, A. Bunde and H. E. Stanley, 2002:

Multifractal detrended fluctuation analysis of nonstationary time series , *Physica A* **316**, 87-114.

Mallat S.G., 1999: *A Wavelet Tour of Signal Processing* (2nd edition), Academic Press, Cambridge.

Mandelbrot B.B., 1983: *The Fractal Geometry of Nature*, Freeman, New York.

Peng C.-K., S.V. Buldyrev, S. Havlin, M. Simons, H.E. Stanley, and A.L. Goldberger, 1994: Mosaic organization of DNA nucleotides, Phys. Rev. E **49**, 1685-1689.

Peng C.-K., Mistus J., Hausdorff J.M., Havlin S., Stanley H.E. Goldberger A.L., 1999: Long-range anticorrelations and non-Gaussian behavior of the heartbeat, *Phys. Rev. Lett.* **70**, 1343-1346.

Scafetta N., and P. Grigolini, 2002: Scaling detection in time series: diffusion entropy analysis, Phys. Rev. E **66**, 036130.

Scafetta N., Griffin L., West B.J., 2003: Hölder exponent spectra for human gait, *Physica A*, **328**, 561-583.

Struzik Z.R., 2000: Determining Local Singularity Strengths and their Spectra with the WaveletTransform*, Fractals,* **82**, 163-179.

West B.J., Zhang R., Sanders A.W., Miliyar S., Zucherman J.H. Levine B., 1999: Fractal Fluctuations in Cardiac Time Series, *Physica A,* **270,** 552-566.

West B.J., Goldberger, A.L., 1987: Physiology in fractal dimensions, *American Scientist* **75**, 354-364.

West, B.J., 1990: *Fractal Physiology and Chaos in Medicine*, World Scientific, Singapore. West B.J. and N. Scafetta, 2003: A nonlinear model for human gait, *Phys. Rev. E* **67**, 051917-1.

West B.J., N. Scafetta, W.H. Cooke, and R. Balocchi, 2004: Influence of progressive central hypovolemia on Hölder exponent distributions of cardiac interbeat intervals, *Ann. Biomed. Eng*, **32**, 1077-1087.